Coxsackie B viruses and the post-viral syndrome: a prospective study in general practice

B.D. CALDER, MRCGP

P.J. WARNOCK, BSc, MRCGP

R.A. McCARTNEY, FIMLS

E.J. BELL, BSc, PhD, MRCPath

SUMMARY. In a prospective study sera from 140 patients with symptoms suggesting a post-viral syndrome and sera from 100 controls were tested for neutralizing antibodies to Coxsackie B viruses. Sixty-five of the patients (46%) and 25 of the controls (25%) had significant antibody titres. The 65 positive cases who had presented with symptoms were followed up and retested six months later and again after one year. Of these 65 patients 36 (55%) were still unwell after one year and high antibody titres persisted in all but two of the patients. Recovery was not found to correlate with a fall in antibody level, but was more rapid in patients whose presenting symptoms were paraesthesiae, anorexia or dyspnoea. The importance of correctly identifying patients with the post-viral syndrome, who may otherwise be labelled neurotic, is emphasized.

Introduction

COXSACKIE B viruses are endemic in the British Isles and have long been associated with Bornholm's disease and with acute myocarditis and pericarditis. Controlled studies of patients with suspected viral heart disease carried out between 1966 and 1971[1] showed that at least half the cases of acute myocarditis and one third of the cases of non-bacterial pericarditis were associated with Coxsackie B infections. Most of these conclusions were based on the interpretation of static high neutralizing antibody titres, since most patients present too late for virus isolation or the detection of significant rising neutralizing antibody titres which imply recent systemic infection.

Recently associations have been found between Coxsackie B infection and a more chronic multisystem illness. A similar illness, usually reported in epidemic form, has been variously referred to as epidemic neuromyasthenia, epidemic myalgic encephalomyelitis, Iceland disease or Royal Free disease, depending on where, and by whom the diseases were described.[2] This illness, which has often been dismissed as hysteria by sceptics, was fully investigated in 1978 by a symposium at the Royal Society of Medicine. Their findings[3] indicated that there was little evidence in favour of a hysterical phenomenon. On the contrary, the majority of the data pointed towards an organic basis. The condition has been concisely reviewed by Behan.[4] Several reports have linked this syndrome with evidence of recent Coxsackie B infection[5-7] and the long-term evidence of recent Coxsackie B infection has been discussed.[8] Another recent investigation of 50 cases by Behan[9] supports the organic nature of this condition.

In a previous study,[7] we reported a retrospective survey in our own practice of a group of patients, mainly young adults, with a variety of puzzling symptoms. An unexpectedly high proportion of these patients — 38 of 81 tested (47%) — had significant antibody titres to Coxsackie B viruses. On the basis of these findings a prospective study was set up to investigate patients presenting with symptoms suggesting a post-viral syndrome. The aim of this study was to confirm the continuing relationship between Coxsackie B virus antibody titres and a specific clinical syndrome, following up those patients with significant high titres at six months and one year, monitoring clinical progress and antibody levels. We were also interested in any sociological, haematological or biochemical associations between a clinical syndrome and Coxsackie B viruses and in any feature which gave a reliable prognostic indication.

Method

The study practice has 10 000 patients, half the population of Helensburgh, a seaside town on the Firth of Clyde. Over the six month period 1 July to 31 December 1983, 140 patients presenting with symptoms suggesting a post-viral syndrome were entered into the study. Patients whose Coxsackie B virus antibody status had already been investigated were not entered. Fifty-three patients (38%) were male and 87 female (62%). The mean age of the patients was 41 years, with a range of 8–74 years, although most were aged between 25 and 50 years. Blood samples were taken on the day of presentation in 58% of cases and within one week in 66%. A full blood count was carried out and Coxsackie B virus antibody levels and erythrocyte sedimentation rates were determined. Blood film and liver function tests were carried out using the complement fixation test. A serological screen was performed against influenza A and B, the adenovirus group, *Mycoplasma pneumoniae,* psittacosis-lymphogranuloma venereum, Q-fever, leptospirae, the herpes group, mumps and measles.

Coxsackie B virus antibody levels were estimated in 100 control patients. Thirty-seven of the controls were male and 63 female. The mean age was 40 years, with a range of 7–83 years, although most were aged between 20 and 50 years. Thirty-seven of the controls were having blood taken during the study period for some other reason — these were antenatal, trauma, hypertension, anaemia or anticoagulant therapy cases. Patients with acute infections or possible autoimmune conditions were excluded from the control group.

An experienced registered general nurse interviewed and completed a questionnaire for all patients positive for Coxsackie B virus who had presented with symptoms as soon as possible after serological results were available. She completed further questionnaires and took blood samples for repeat Coxsackie B virus serology six months and one year after the initial test. The medical records of the positive patients were traced where possible and examined for details of associated diseases.

Questionnaire

The questionnaire asked for the following basic information: age; occupation; marital status; number of children, if any; geography of home, work, school, social contacts, playgroups,

B.D. Calder, General Practitioner, Helensburgh, Dunbartonshire; P.J. Warnock, Surgeon Lieutenant Commander, Royal Navy; R.A. McCartney, Chief Medical Laboratory Scientific Officer, and E.J. Bell, Top Grade Virologist, Regional Virus Laboratory, Ruchill Hospital, Glasgow.

© *Journal of the Royal College of General Practitioners,* 1987, 37, 11-14.

church, sports activities and so on; foreign travel; allergies; contact with infectious mononucleosis; contact with Coxsackie B virus; household pets. The questionnaire also asked about the following specific symptoms: fatiguability, tiredness, sweating, lightheadedness, headaches, palpitations, chest pain, dyspnoea, myalgia, vertigo, dizziness, depression, anxiety, poor concentration, panic attacks, anorexia, vomiting, diarrhoea, paraesthesiae, slurred speech and paralysis, differentiating between those offered spontaneously and those revealed by direct enquiry. As much volunteered information as possible was elicited before leading questions were asked. At the six-month and one-year follow-up interviews patients were asked if they had completely recovered. If they replied yes they were asked how long they had felt unwell. If no they were asked what they felt was still wrong with them. The patients were also asked to provide the interval between the onset of symptoms and their initial consultation.

Results from the questionnaire were processed using Glasgow University's ICL 2988 computer and associations sought by cross tabulation.

Coxsackie B virus serology

All the Coxsackie B virus antibody tests were performed blind at the Regional Virus Laboratory, Ruchill Hospital. The sera were tested against Coxsackie B viruses 1–5 using the micrometabolic inhibition test and hela cells described elsewhere.[10] By 1985 supplies of hela cells had become unreliable. A modification of this microtitre test was introduced using vero cells and the end points of serum titrations determined by microscopic examination for cytopathic effects rather than by colour range. All sera from each patient were tested in parallel to avoid test to test variation. As in previous studies,[1,11] a fourfold rise/fall in titre or titres of 512 and above were regarded as indicative of recent Coxsackie B virus infection and titres of 256 as suggestive of recent infection. Titres of 128 to Coxsackie B1, B3 and B5 viruses, suggesting recent infection were also included.

Results

Of the 140 ill patients 65 (46%) were found to be Coxsackie B virus antibody positive and 25 of the 100 controls were also positive ($P<0.01$) (Table 1). The 65 ill patients who were antibody positive were approached for follow up and 63 initial questionnaires were completed (one patient refused and one was untraceable). Three more patients were lost to follow up at six months and one further patient at one year — all four had moved from the area. None of the controls who were antibody positive developed symptoms suggesting post-viral syndrome within the year of the study. The results given below refer to the 65 ill patients. Of these 65 patients 25 (38%) were male; the mean age was 42 years with a range of 8–74 years, although most were aged between 25 and 50 years.

Common factors linking the positive cases were sought but no associations were found implicating geography (work or home), foreign travel, household pets or allergies. Three patients had recently been in contact with patients with infectious mononucleosis but no other contacts with infectious diseases were apparent. In two cases close members of the family had positive Coxsackie B virus antibody titres, but no other connections between the patients were found.

Table 1. Results of Coxsackie B virus neutralizing antibody titres.

Coxsackie B virus antibody titre	No. (%) of samples	
	Patients ($n=140$)	Controls ($n=100$)
⩾512	31 *(22)*	9 *(9)*
256	27 *(19)*	14 *(14)*
128[a]	7 *(5)*	2 *(2)*
Total	65 *(46)*	25 *(25)*

[a] Coxsackie B1, B3 and B5 viruses only.

Table 2. Frequency of occurrence of positive titres[a] for the various Coxsackie B virus serotypes. The pattern among the controls is given for comparison.

Serotype	No. of patients			No. of controls
	At onset	After six months	After one year	
B1	4	4	3	2
B2	17	13	13	6
B3	6	5	5	2
B4	36	36	36	13
B5	2	2	2	2
Total	65	60	59	25

[a] 256 and above in the case of Coxsackie B2 and B4 viruses and 128 and above in the case of Coxsackie B1, B3 and B5 viruses.

Table 3. Frequency of different Coxsackie B virus antibody levels found initially and at six-month and one-year follow-up.

Coxsackie B virus antibody titre	No. of patients		
	At onset	After six months	After one year
<64	0	2	2
128	7	9	7
256	27	17	17
512	16	14	13
⩾1024	15	18	20
Total	65	60	59

The social class distribution of the patients — nine (14%) in group 1, 14 (22%) in group 2, 29 (45%) in group 3, 11 (17%) in group 4 and two (3%) in group 5 — broadly reflected the social class structure of the practice. In contrast to the earlier retrospective study[7] where only three out of 38 cases (8%) were in Armed Forces families, in the present study 14 cases (22%) occurred in this group which approximates more closely to the proportion of Armed Forces families in the practice.

There was considerable variation in the interval between the onset of symptoms and initial consultation — 18 patients (28%) consulted less than 24 hours after the onset of symptoms, 26 (40%) in less than a week and 42 (65%) in less than a month.

The frequency of occurrence of the various serotypes and the antibody levels are shown in Tables 2 and 3. The serotype B4 was the most common, followed by B2, and the same pattern was seen in the controls. Fourteen patients (22%) had mildly deranged liver function tests (elevated transaminases) and 29 (45%) were reported as having abnormal lymphocyte levels.

The medical records of all but one of the 65 patients were traced and no obvious associated diseases were found. Routine viral screens on all 65 samples were negative with the exception of one measles titre of 512.

As expected, direct questioning revealed additional symptoms to those volunteered spontaneously and this disparity was due mainly to an increase in less definable symptoms such as poor concentration, lightheadedness, panic attacks and anxiety (Figure 1). An unexpected feature was the increased reporting of slurred speech on direct enquiry. A similar pattern of increased response to all symptoms on direct questioning was seen at six

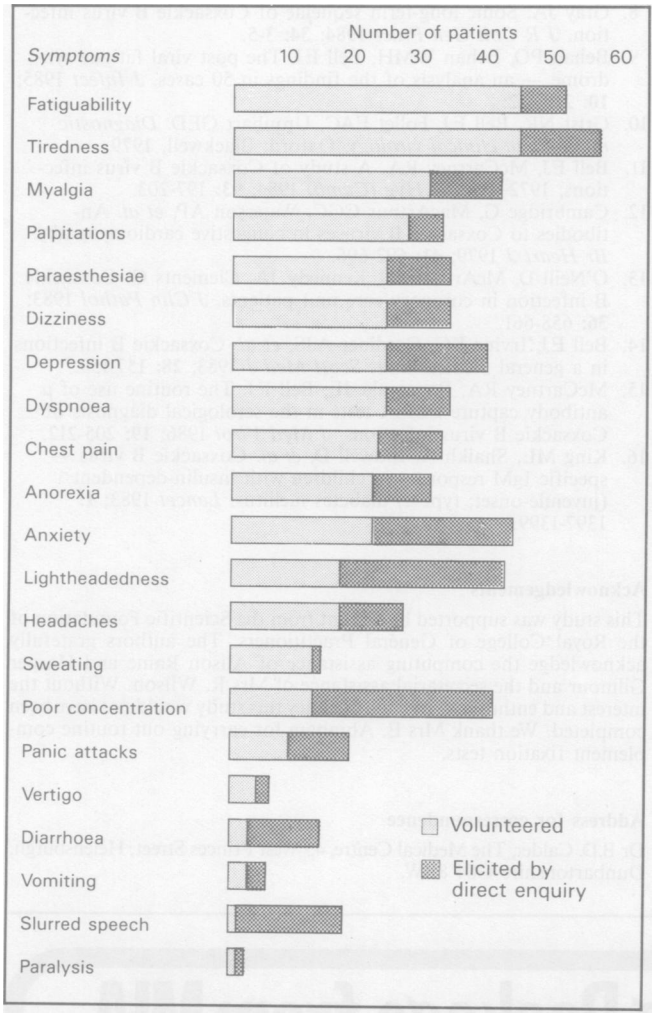

Figure 1. *Frequency of symptoms at onset, showing volunteered symptoms and those elicited by direct questioning (n = 63).*

months and one year. The frequency of presenting symptoms spontaneously offered at onset and their frequency at six months and one year are shown in decreasing order of frequency at onset in Table 4. Although some symptoms were much more common than others, there was no symptom or group of symptoms which was sufficiently common to be of specific diagnostic value. Forty seven of the original 65 patients (72%) considered themselves to be still unwell at the six-month follow-up compared with 36 (55%) at the one-year follow-up.

From cross tabulation of the results it was found that no specific feature (abnormal liver function tests, abnormal lymphocyte levels, specific viral serotypes or high antibody titres) predicted a better or worse prognosis. However, certain presenting symptoms appeared to be associated with a more favourable outcome; more than 70% of patients presenting with paraesthesiae, anorexia and dyspnoea had lost these initial symptoms within six months (Table 4). After one year the antibody levels had returned to non-significant levels in only two of the 65 patients tested. Therefore clinical improvement did not correlate with a fall in titre.

Discussion

The suggestion that the higher the Coxsackie B virus antibody titre the more likely it is that the infection is recent has proved useful in clarifying the role of Coxsackie B viruses in adult heart disease.[1,12,13] In illness with a chronic relapsing course, such as recurrent atypical chest pain, static high titres persisting three or more years were observed,[11] thus making interpretation of their significance more difficult. This study has confirmed our earlier finding[7] that there is a group of symptoms which are associated with evidence of Coxsackie B infection. We have also shown that clinical improvement is slow and recovery does not correlate with a fall in Coxsackie B virus antibody titre. To our knowledge, no follow-up studies of antibody levels over one year have previously been reported. We suggest that some of the patients who presented with similar symptoms but were found to be negative for Coxsackie B virus antibodies may be infected by other as yet unidentified viruses. Behan's recent study[9] linked evidence of Coxsackie B infection with disordered immune responses.

Positive Coxsackie B virus antibody titres, especially those of 512 and above were detected more frequently in the control group than in previous studies,[13,14] and this may signify a high incidence of infection in the study practice, at least during the study period.

Control sera taken from more than 1000 healthy adults in the West of Scotland between 1973 and 1984 showed that 4–5% had titres of 512 and above and 10–12% titres of 256.[14,15] However, of 100 samples taken from women for rubella susceptibility testing in the area of the Vale of Leven District General Hospital (our district general hospital) in June 1983 13 showed Coxsackie B virus antibody titres of 512 and above and 27 showed titres of 256 and above (Riding MM. Personal communication). The latter levels are similar to those found in the control group in this study.

A reliable assay for the detection of Coxsackie B virus specific immunoglobulin (Ig)M, the presence of which implies recent (or persisting) infection, could have provided a more precise serological diagnosis but was unfortunately not available at the start of this study in 1983. King and colleagues[16] described a μ antibody capture Coxsackie B virus specific IgM enzyme-linked immunosorbent assay (ELISA) test which they used to investigate the role of these viruses in acute juvenile onset diabetes mellitus.

Table 4. Frequency of spontaneously offered symptoms at onset and at the two follow-ups.

Symptoms	No. of patients complaining		
	At onset ($n=63$)	After six months ($n=60$)	After one year ($n=59$)
Fatiguability	45	30	23
Tiredness	45	34	29
Myalgia	31	17	15
Palpitations	28	10	11
Paraesthesiae	24	5	8
Dizziness	24	10	10
Depression	24	18	10
Dyspnoea	24	7	9
Chest pain	23	12	14
Anorexia	22	6	6
Anxiety	21	16	12
Lightheadedness	18	7	6
Headaches	18	9	10
Sweating	13	5	2
Poor concentration	13	9	14
Panic attacks	9	7	5
Vertigo	4	2	2
Diarrhoea	3	1	3
Vomiting	3	0	0
Slurred speech	1	0	0
Paralysis	1	1	1

In 1985 this technique was adopted by the Regional Virus Laboratory at Ruchill for the rapid, routine serological diagnosis of Coxsackie B infection in cardiac and relapsing illnesses suspected to be caused by Coxsackie B virus.[15]

Treatment has not been addressed in this study. As found previously, beta-blocking agents were effective for troublesome palpitations, and rest generally appeared beneficial. Once again we stress the importance of recognizing this relatively common illness, which may easily be mistaken for psychoneurosis. If a previously fit and uncomplaining individual presents with protracted vague or suggestive symptoms, then the possibility of the post-viral syndrome should be considered. These patients can experience great relief when an organic rather than a psychological basis for their symptoms is suggested. This is best achieved if virological investigation is instigated early in the patient's illness. We look forward to further clarification of the aetiology of this distressing condition.

References

1. Grist NR, Bell EJ. A six year study of Coxsackie B infections in heart disease. *J Hyg (Camb)* 1974; **73:** 165-172.
2. Anonymous. Epidemic myalgic encephalomyelitis. *Br Med J* 1978; **1:** 1436-1437.
3. Ramsay AM. Epidemic neuromyasthemia 1934–1977: current approaches. *Postgrad Med J* 1978; **54:** 704-774.
4. Behan PO. Epidemic myalgic encephalomyelitis. *Practitioner* 1980; **224:** 805-807.
5. Fegan KG, Behan PO, Bell, EJ. Myalgic encephalomyelitis — report of an epidemic. *J R Coll Gen Pract* 1983; **33:** 335-337.
6. Keighley BD, Bell EJ. Sporadic myalgic encephelomyelitis in a rural practice. *J R Coll Gen Pract* 1983; **33:** 339-341.
7. Calder BD, Warnock PJ. Coxsackie B infection in a Scottish general practice. *J R Coll Gen Pract* 1984; **34:** 15-19.
8. Gray JA. Some long-term sequelae of Coxsackie B virus infection. *J R Coll Gen Pract* 1984; **34:** 3-5.
9. Behan PO, Behan WMH, Bell EJ. The post viral fatigue syndrome — an analysis of the findings in 50 cases. *J Infect* 1985; **10:** 211-222.
10. Grist NR, Bell EJ, Follet EAC, Urquhart GED. *Diagnostic methods in clinical virology.* Oxford: Blackwell, 1979.
11. Bell EJ, McCartney RA. A study of Coxsackie B virus infections, 1972–1983. *J Hyg (Camb)* 1984; **93:** 197-203.
12. Cambridge G, MacArthur CGC, Waterson AP, *et al.* Antibodies to Coxsackie B viruses in congestive cardiomyopathy. *Br Heart J* 1979; **41:** 692-696.
13. O'Neill D, McArthur JD, Kennedy JA, Clements G. Coxsackie B infection in coronary care unit patients. *J Clin Pathol* 1983; **36:** 658-661.
14. Bell EJ, Irvine KG, Gardiner AJS, *et al.* Coxsackie B infections in a general medical unit. *Scott Med J* 1983; **28:** 157-159.
15. McCartney RA, Banatvala JE, Bell EJ. The routine use of μ antibody capture ELISA tests in the serological diagnosis of Coxsackie B virus infections. *J Med Virol* 1986; **19:** 205-212.
16. King ML, Shaikh A, Bidwell D, *et al.* Coxsackie B virus — specific IgM responses in children with insulin-dependent (juvenile-onset; type 1) diabetes mellitus. *Lancet* 1983; **1:** 1397-1399.

Acknowledgements

This study was supported by a grant from the Scientific Foundation of the Royal College of General Practitioners. The authors gratefully acknowledge the computing assistance of Alison Raine and Harper Gilmour and the secretarial assistance of Mrs R. Wilson. Without the interest and enthusiasm of Tina Yockney this study would not have been completed. We thank Mrs E. Abraham for carrying out routine complement fixation tests.

Address for correspondence

Dr B.D. Calder, The Medical Centre, 45 West Princes Street, Helensburgh, Dunbartonshire G84 8BW.